RESEARCH

Diabetes mellitus management in the context of cranial tumors

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The study of the relationship between cancer and diabetes mellitus (DM) has been under investigation for many decades. Particularly in the field of neurology and neurosurgery, increasing emphasis has been put on the examination of comorbid DM in patients with cranial tumors. Namely, as the most common and invasive type of malignant adult brain tumor, glioblastoma (GBS) has been the focus of said research. Several mechanisms have been described in the attempt to elucidate the underlying association between DM and GBS, with the metabolic phenomenon known as the Warburg effect and its consequential downstream effects serving as the resounding culprits in recent literature. Since the effect seen in cancers like GBS exploits an upregulated form of aerobic glycolysis, the role of a sequela of DM, known as hyperglycemia, will be investigated. In particular, in the treatment of GBS, surgical resection and subsequent chemotherapy and/or radiotherapy are used in conjunction with corticosteroid therapy, the latter of which has been linked to hyperglycemia. Unsurprisingly, comorbid DM patients are significantly susceptible to this disposition. Further, this fact is reflected in recent literature that demonstrates the impact of hyperglycemia on cancer advancement and patient outcomes in several preclinical and clinical studies. Thus, this review will aim to underline the significance of diabetes and glycemic control via standard-of-care treatments such as metformin administration, as well as to describe emerging treatments such as the signaling modulation of insulin-like growth factor and the employment of the ketogenic diet.

Keywords: diabetes mellitus (DM), glioblastomas (GBS), hyperglycemia, Warburg effect, glucocorticoids, diabetes management, ketogenic diet, IGF-1 pathway

Introduction

Cancer, specifically that of the brain and central nervous system, accounts for a substantial proportion of morbidity and mortality in the United States and worldwide [1]. This fact is due to brain cancer's complex pathogenesis and mechanisms of action within the body. Among the numerous types of brain tumors, glioblastomas (GBS) are the most common, accounting for 49.1% of all recorded primary, malignant brain tumors [2, 3]. Thus, GBS will serve as a model for the subsequent discussion on the interaction between cranial tumors and the management of one of the most significant chronic disease burdens in the United States—diabetes mellitus (DM) [4].

As mentioned earlier, cancer is a formidable disease that manifests itself in almost every organ system and

physiological process, with energy metabolism serving as a key area of study for many decades [5]. Specifically, a major biochemical hallmark of tumor cells is the disruptive alteration from oxidative phosphorylation to aerobic glycolysis, termed the Warburg effect [6]. Many preclinical and clinical studies have shown that hyperglycemia is associated with a worse prognosis in comorbid cancer patients with DM compared to their non-diabetic counterparts.

In this regard, it is imperative to manage plasma glucose levels in order to effectively curb the underlying molecular mechanism for said impact in the context of comorbid patients afflicted with DM and cranial tumors. To that end, an interesting contraindication can be observed when comorbid patients are prescribed corticosteroids for the treatment of their cancer because it has the potential to disrupt glucose control [7]. Therefore, the objective of this study is to discuss

diabetes management in the context of steroid administration for cranial tumors, i.e., GBS, and to highlight emerging treatment options to ultimately improve patient outcomes.

Diabetes mellitus and Glioblastomas

Together, cancer and diabetes are amongst the leading causes of morbidity and mortality globally (8). A diagnosis of a cranial tumor alone, such as GBS, accounts for 57% of all gliomas, with a 5-year survival rate of only 5.8% (2).

Thus, comorbid with a disease such as DM, which is estimated to afflict approximately 700 million people by 2045 and is already responsible for 15.9% of morbidity in the United States, the study of the association between the two has become increasingly important for the identification of therapeutic targets and effective management (9).

As a disease characterized by uncontrolled and elevated levels of plasma glucose, known as hyperglycemia, this aspect of DM has been suspected to be the main contributor to the poorer prognosis observed in comorbid patients. According to Supabphol and colleagues, several studies have demonstrated that clinical outcomes depend solely on the level of glycemic control in cancer patients, regardless of DM status.

For example, a statistical analysis of a large cohort of 301,948 participants, aged 16–95 years and filtered for known diabetes, was followed up with several years after a health checkup to reveal that patients with elevated plasma glucose suffered significantly more cancer-related deaths (HR: 1.17; 95% CI: 1.03–1.34; $p < 0.05$) (10). Furthermore, when specifically looking at the impact of hyperglycemia on prognosis in comorbid GBS patients, it was found to confer a statistically significant poorer outcome on overall patient survival (HR, 1.671; $p < 0.001$) (11).

In sum, the aforementioned statistics suggest that hyperglycemia is implicated in the molecular mechanisms fundamental to the link between DM and cranial tumors such as GBS. Consequently, the proceeding discussion will attempt to highlight the metabolic utility of glucose and its role in malignancy (12).

Cancer and glucose metabolism

The deregulation of cellular energetics in cancer cells dates back nearly a century, when Otto Warburg observed increased glucose uptake and subsequent fermentation of glucose to lactate in mammalian cells even in the presence of aerobic conditions (13). This metabolic rewiring was termed the "Warburg effect" in the early 1970s and was originally thought to be a consequence of mitochondrial dysfunction (14).

Although this hypothesis was proven partially incorrect, the experimental observations helped lead to the discovery that upregulated glycolysis in cancer metabolism is owed to the excess energy demand of the cells, as well as for the biosynthesis of carbohydrates, fats, and proteins (15). Moreover, an important means to that end is the synthesis of glycolytic precursors, which effectively block the negative feedback loop on adenosine triphosphate (ATP) by preventing the accumulation of nicotinamide adenine dinucleotide (NADH)—a powerful modulator of glycolysis (16).

Consequently, this unique feature of cancer cell metabolism facilitates the synthesis of ATP at an accelerated rate and is speculated to explain why they consume more glucose as compared to normal cells. This phenomenon is particularly advantageous for malignant cells because it ultimately confers a selective advantage in promoting proliferation, survival, and long-term maintenance (13).

In the context of brain cancer, such as cranial tumors, the preceding metabolic mechanisms hold true as a defining hallmark of GBS (17). This upregulated glycolytic switch in cancerous brain tissue has fatal consequences, especially because it is responsible for 60% of our daily glucose intake despite accounting for only 2% of total body weight (18).

Specifically, the central nervous system microenvironment allows for increased glucose utilization via the Warburg effect, which has multiple downstream effects that allow for tumorigenesis and enhanced invasiveness via an acid-mediated invasion hypothesis and signal transduction modulation through radical oxygen species and/or chromatin acetylation (19–21). As seen in **Figure 1**, these events are particularly attractive because they identify a direct role for altered glucose metabolism in promoting metastasis, a deadly characteristic of GBS (13).

Thus, it is not a novel insertion to point out the negative impact hyperglycemia can have on individuals afflicted with a cancer such as GBS and can help explain its prognostic significance. In the following discussion, a few standard-of-care approaches to the treatment of GBS will be highlighted, as well as their combined use with a corticosteroid—with the latter being of particular relevance due to its hyperglycemia-inducing properties (11).
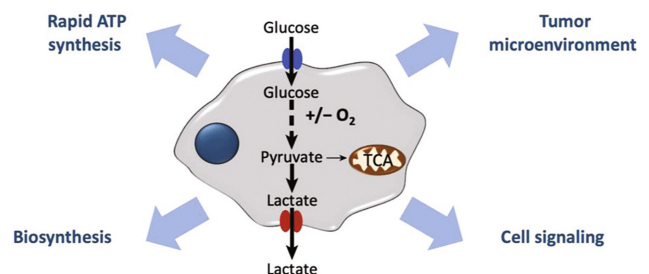

FIGURE 1 | Summary of observed roles of the Warburg effect. The Warburg effect, which is described as the increased degree of aerobic glycolysis and the preferential synthesis of lactate, confers malignancies such as GBS with the ability to rapidly grow, proliferate, and survive. The functions through which these events occur have been summarized (13).

Standard approaches to cranial tumor treatment

Surgical resection

Currently, the majority of patients with GBS receive neurosurgical intervention in the form of surgical resections with standard craniotomies under general anesthesia (22, 23). The purpose underlying these procedures is to excise as much tumor tissue as safely possible—in order to reduce its associated pathogenic effects—and to obtain sufficient amounts of tissue to conduct histological analysis (23, 24). Traditionally, surgical resection entailed performing a craniotomy on the affected patient (22, 25). Contingent on the location of the tumor, the patient can either be awake during the procedure or sedated under general anesthesia (22, 25). Awake procedures are generally restricted to cases where the glioma is located at the pre-central gyrus, Wernicke's area, Broca's area, and/or the brain stem—all areas that can be mapped intraoperatively with cortical stimulation for language and sensorimotor function (22, 25–27).

This mapping allows for better distinction between tumoral tissue and normal, functional brain parenchyma and is thought to achieve tumor removal more precisely as compared to standard craniotomy procedures (22, 26–28). Consequently, this higher precision has led to improved post-operative outcomes (**Figure 2**).

Otherwise, intraoperative surgical guidance is conducted with pre-operative diffusion tensor imaging (DTI) via magnetic resonance imaging (MRI), which allows for the visualization of subcortical white matter tracts in multiple planes, or functional MRI (fMRI), which identifies functional regions based on increased regions of blood flow seen on the MRI image (**Figure 3**) (22, 29).

As with any form of resection, this procedure is a delicate balance between maximizing the amount of tumor removed while preserving the patient's functional status (30). Many of the factors that are considered when determining the excision threshold include the patient's age, tumor location within the brain, neurological symptoms, and comorbidities such as cerebral edema, cardiovascular disease, and incidents of deep vein thrombosis (30–32).

Historically, patients have been evaluated for pre-operative candidature based on age and the Karnofsky Performance Score (KPS) (22, 33), which assesses the physical ability of the patient to independently complete routine tasks and can be used to predict post-operative outcomes. However, KPS fails to capture the presence and effects of the aforementioned comorbidities (33–35).

Thus, there is certainly room for improvement in predicting post-operative success by including these additional factors. In fact, recent studies have purported the need to combine KPS evaluation with measures such as the Charlson Comorbidity Index (CCI) to elucidate operative
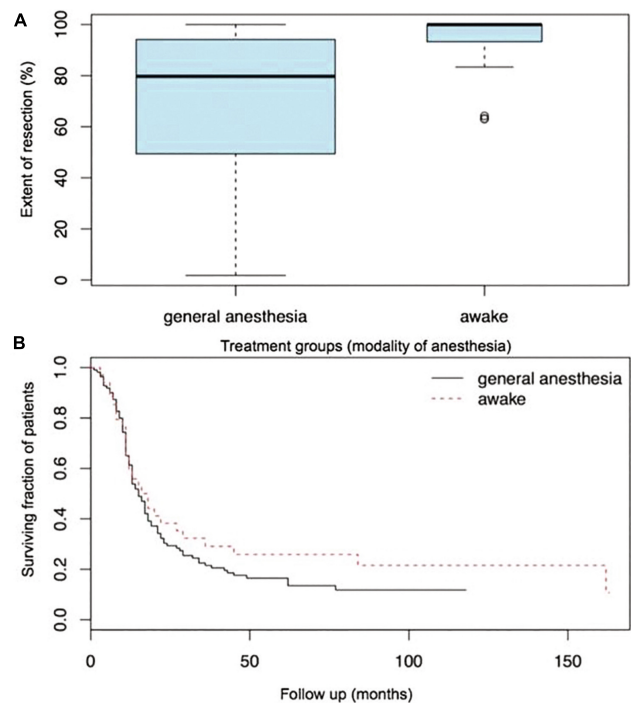
FIGURE 2 | Operative differences between awake and standard surgical resections. **(A)** Box plot depicting the extent of resection (EOR) in patient groups of either general anesthesia craniotomy or awake craniotomy in a retrospective matched case-control study. Awake procedures achieve greater EOR (median for awake: 100%; median for general anesthesia: 79.73%; $p < 0.0001$, Mann–Whitney test) with much less variability as compared to general anesthesia procedures. **(B)** Kaplan–Meier curves depicting post-operative survival for patient groups of either general anesthesia craniotomy or awake craniotomy. Awake procedures depict a trend of a greater proportion of patients surviving during a longer period (median for awake: 17 months; median for general anesthesia: 15 months), yet results are not significant ($p = 0.297$, $\chi^2 = 1.1$) (28).

risk and better determine the candidature of patients with GBS (33, 34, 36).

Among possible treatment options for GBS, the amount of tissue excised with surgical resection has the most prognostic impact on patient survival, with multiple sources stating that a minimum of 70% extent of resection (EOR) has a significant impact on improved survival with minimal recurrence (22, 26, 37, 38).

Furthermore, Proescholdt et al. found that 72.5% of studies report beneficial outcomes following surgical resection (39), highlighting its effectiveness in treating an aggressive disease like GBS.

Chemotherapy and radiotherapy

Patients typically receive additional treatment after surgical resection, such as chemotherapy and radiation therapy (22). Bevacizumab and temozolomide (TMZ)-40 are currently the most effective GBS treatments (40). Bevacizumab, an anti-VEGF antibody that is indicated for newly diagnosed and
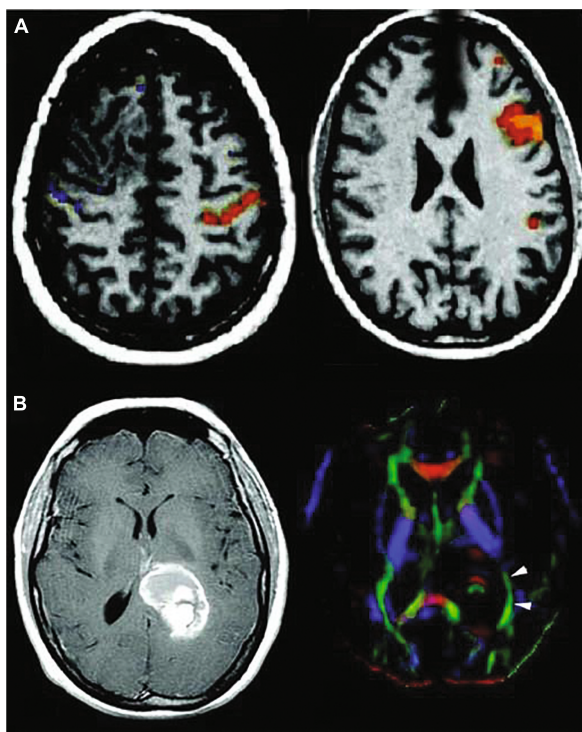
FIGURE 3 | Pre-operative neuronavigation techniques for standard surgical resection. **(A)** (**Left**) Functional magnetic resonance imaging (fMRI) displaying highlighted regions of the motor cortex while a patient taps their finger. The blue region corresponds to the right central sulcus and the red region corresponds to the left central sulcus. (**Right**) fMRI displaying highlighted regions of the speech cortex while the patient speaks in a task. Red region corresponds to Broca's area. **(B)** (**Left**) T1-weighted MRI scan depicting a tumor near the thalamus (white mass). (**Right**) Diffusion-tensor image (DTI) of the same patient showing white matter tracts. The colors represent directionality of the tracts: Red is **left/right**, blue is ascending/descending, and green is anterior/posterior (25).

recurrent GBS, has been shown to increase progression-free survival in patients, although it has no effect on the overall survival rate (40–42).

The mechanism of action for TMZ involves leveraging its alkylating nature to methylate cellular DNA, causing DNA damage and inducing cell death (22, 43). When given concomitantly with radiotherapy, TMZ was found to extend the median survival time from approximately 12.2 to 14.6 months (43, 44).

Radiotherapy is the standard treatment for patients with unresectable GBS, as well as adjuvant care for post-resection (45). Radiotherapy involves delivering an external radiation beam, usually photons, using a linear accelerator, which induces DNA damage and cell death in tumor tissue (46, 47).

Steroid use with standard Glioblastoma treatment

Glucocorticoid drugs are additionally utilized in the treatment of patients with GBS. Glucocorticoids, such as

dexamethasone at 8–16 mg a day, are often pre-scribed perioperatively during radiotherapy to manage vasogenic cerebral edema and associated symptoms that often present with GBS (48, 49). In the context of surgical resection, glucocorticoids are administered to patients to prevent severe consequences of surgical stress, such as adrenal insufficiency or hemodynamic instability (50).

Additionally, glucocorticoids have demonstrated efficacy in reducing pain, nausea, and vomiting associated with GBS tumors and have an increasing effect on patient appetite (51). Typically, higher doses of glucocorticoids are reserved for GBS patients who have larger tumors and more severe neurological deficits (52).

Despite their effectiveness in managing GBS-related symptoms, the possible adverse effects of glucocorticoids cannot be understated. Prolonged use of glucocorticoids has been found to commonly induce blurred vision, myopathy, tremor, behavioral changes, and many more other systemic effects (49, 51, 52). However, many of these effects can resolve upon cessation (52).

One of the most serious side effects of glucocorticoid administration is the exaggerated effect on patient blood glucose levels (53). In fact, the effect of prolonged glucocorticoid administration is strong enough to cause diabetes in patients who have never had hyperglycemia (54). Interestingly, there are many mechanisms of action that enable glucocorticoids to elevate serum sugar levels.

Glucocorticoids, in particular, can disrupt insulin signaling cascades and promote protein catalysis and amino acid release, all of which can prevent insulin action on the skeletal muscle glucose transporter type 4 (GLUT4) and reduce glucose uptake by 30–50% (54, 55). Along with inducing insulin resistance, glucocorticoids are believed to induce apoptosis in pancreatic beta cells and reduce the number of GLUT2 transporters, effectively hindering pancreatic insulin production (54, 56).

Thus, in patients already diagnosed with DM and even in patients with no prior history, it is of the utmost importance to monitor blood sugar levels if glucocorticoids are to be administered. Of note, if a patient with GBS begins to exhibit hyperglycemic symptoms during treatment or already has DM, endocrinology should be consulted.

Diabetes management in cranial tumors

Diabetes mellitus standard of care

Typically, the first-line treatment for type 2 diabetes mellitus (T2DM) recommended by the American Diabetes Association (ADA) is metformin monotherapy with comprehensive lifestyle modifications, inclusive of weight management and physical activity (57). If patients present

with comorbidities such as atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and/or heart failure (HF), glucagon-like peptide 1 receptor (GLP1R) agonists or sodium–glucose cotransporter 2 (SGLT2) inhibitors with or without concurrent metformin are indicated as initial therapy.

Unless contraindicated or poorly tolerated, metformin therapy should be continued. If the glycemic need persists, combination therapy may be considered for patients. With patients who evidence catabolism, hyperglycemic symptoms, and/or high hemoglobin A1C (HbA1C) (>10%) or blood glucose (300 mg/dL), insulin may be recommended and intensified based on whether the patient meets treatment goals. Further, medication and medication-taking behavior should be assessed every three to 6 months to ensure treatment efficacy and individualization.

Since the hallmark of type-1 diabetes mellitus (T1DM) is beta cell destruction, recommendations include injections of basal and prandial insulin, which may be administered multiple times daily for basal and postprandial glycemic control. Another approach commonly used is continuous insulin infusion, delivered subcutaneously. Regardless of insulin delivery method, patient education on matching mealtime insulin dose to carbohydrate intake is critical for self-efficacy. For older adults, assessment of geriatric syndromes and the induction of polypharmacy, cognitive impairment, and functional impairment (i.e., KPS) may further aid in the assessment of diabetes self-management (57).

Diabetes mellitus, hyperglycemia, and Glioblastoma treatment considerations

Diabetes management is extremely important in cancer patients. Patients diagnosed with cancer and T2DM, for example, have a 41% higher risk of long-term mortality from any cause than patients diagnosed with cancer without diabetes, according to Barone and colleagues (58). Moreover, studies suggest the prevalence of T2DM in GBS patients to be ~16% (59–61).

However, evidence suggesting a relationship between diabetes status and cranial tumor outcomes is still controversial. Montemurro and colleagues (62) found that the majority of the literature shows no relationship between T2DM and overall survival in GBS patients. However, meta-analyses do point toward decreased overall survival in GBS patients with hyperglycemia, independent of diabetes status (HR, 1.671; $p < 0.001$) (11).

Specifically, Tieu and colleagues showed that overall survival in GBS patients with blood glucose levels 113 mg/dL treated with radiation and TMZ was 16 months, compared to 13 months for patients with blood glucose levels 113 mg/dL and lower undergoing similar treatment (**Figure 4**) (63). Similarly, Welch and Grommes found that GBS patients with

a median glucose of 173 mg/dL had an 11-month overall survival compared to 9 months for patients with blood glucose ranging from 174 to 247 mg/dL (64).

Patients in the study by Mayer et al. showed that those experiencing hyperglycemic episodes saw a significant reduction in overall survival of nearly 50%—a degree of negative effect comparable to incomplete treatment per the Stupp protocol (65, 66). Additionally, McGirt et al. showed median survival in persistently hyperglycemic GBS patients undergoing surgical resection to be 5 months, compared to 11 months for the non-hyperglycemic cohort (67).

Interestingly, Derr et al. were able to demonstrate the progressive decline in overall survival when blood glucose levels increased in GBS patients, even after data were adjusted for average daily glucocorticoid dose, age, and KPS at baseline ($p = 0.041$) (68). However, this study was performed prior to the standard use of TMZ. Of note, most studies did not utilize HbA1C, often regarded as a better measure of glycemic control than blood glucose, in their analysis.

Nevertheless, Barami et al. noted a similar pattern in the negative association between HbA1C and overall survival in GBS patients (69). Lastly, this trend was further corroborated by Lui and colleagues in 2022, who were able to stratify the isocitrate dehydrogenase (IDH)-wildtype GBS based on molecular subclass—namely, RTK I, RTK II, and mesenchymal (70). While tumor methylation status was not associated with variations in overall survival ($p = 0.9$), greater glucose levels were associated with shorter overall survival in RTK I ($p = 0.08$) and mesenchymal tumors ($p = 0.05$).

This trend was not seen in the RTK II tumor sub-type ($p = 0.99$). Furthermore, they did not find significant epigenetic or metabolomic alterations amongst GBS tumors in diverse glycemic environments. No paper to date has shown improvement in overall survival in hyperglycemic GBS patients. While the negative effect of hyperglycemia on overall survival is not anomalous for solid state tumors, GBS warrants special consideration as corticosteroid treatment—which is known to have hyperglycemia-inducing effects—is the standard of care for GBS patients (71, 72).

Proposed molecular ramifications of hyperglycemia

The inverse relationship among blood glucose and overall survival in GBS patients appears to be complex with multiple mechanisms. Subtypes of gliomas are shown to have distinct mechanisms of genesis, so the effects of hyperglycemia may be different based on glioma sub-type (73). Furthermore, the distinct pathophysiologies of T1DM vs. T2DM may affect GBS biology differently. One possibility points toward glucose having a direct role in GBS spread through the tumor's ability to take advantage of glucose-dependent metabolism, even with oxygen present (74).
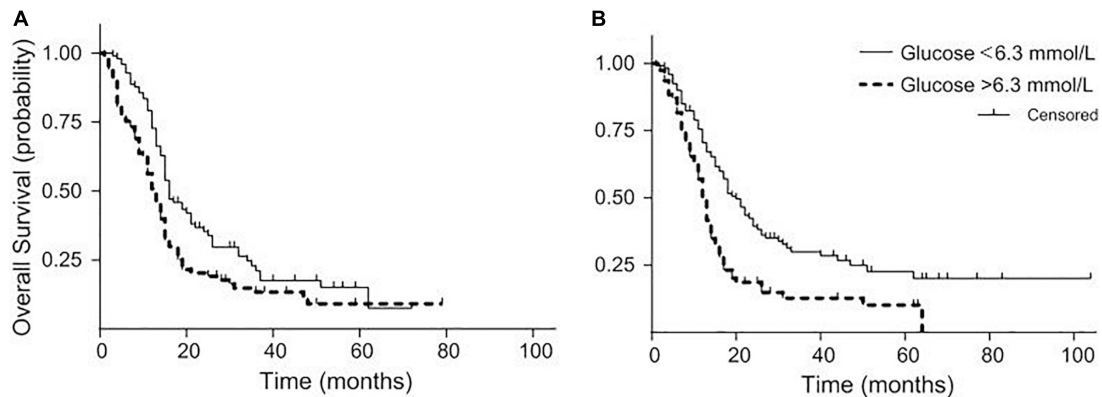
FIGURE 4 | Blood glucose-dependent survivability following temozolomide and radiotherapy. **(A)** Kaplan–Meier curve depicting the survivability of patient groups separated by time-weighted blood glucose concentration (from start of radiotherapy to 4 weeks), following concurrent treatment with temozolomide (TMZ) and radiation. **(B)** Depicts the same as **(A)**, but with a validation group of a similar patient profile. Both plots show an overall increase in survival in the <6.3 mmol/L glucose patient group (median for <6.3 mmol/L: 16 months; median for >6.3 mmol/L: 13 months; $p = 0.03$), **(A)**; $p = 0.005$, **(B)** (63).

Increased intracerebral glucose, known to be seen at higher levels in patients without prior hyperglycemia, may enable enhanced use of metabolic substrates needed for propagation by the tumor cells (75, 76). Given the high glucose consumption of high-grade cranial tumors, Simoes et al. demonstrated in a mouse model that subjects with gliomas experience a 2.5-fold rise in intracerebral glucose after induction of hyperglycemia (77, 78).

In healthy mice, the glucose bolus minimally affected the glucose content in the brain. Hyperglycemia can activate a number of intracellular pathways involved in tumor progression, including pro-proliferation AKT/mTOR signaling, WNT/-catenin signaling, and increased leptin levels (79–81).

Bao et al. recently showed that hyperglycemia upregulated the *in vitro* expression of G-protein coupled chemoattractant formyl peptide receptor 1 (FPR1) and epidermal growth factor receptor (EGFR) in GBS tumor models, both of which are known to enhance tumor malignancy (79). Several investigations report that FPR1 is associated with a poorer prognosis in GBS, and studies in mice have shown tumor malignancy to decrease when FPR1 RNA is targeted (82, 83).

FPR1 and EGFR also aid in the invasiveness of GBS by directly mediating vascular endothelial growth factor (VEGF) formation (79, 84). Interestingly, endogenous FPR1 agonist Annexin A1 (AnxA1) is released by necrotic GBS cells, which has the effect of further activating the live GBS cells within the tumor microenvironment (85).

Another explanation for the inverse relationship among hyperglycemia and overall survival in GBS may be through increased insulin levels. Because GBS expresses the same insulin receptors found in the periphery, hyperinsulinemias caused by hyperglycemia may promote tumor proliferation independently (86–89). Liu et al. discovered increased insulin signaling in conjunction with PI3K-AKT and MAPK upregulation (70, 90).

In addition, hyperinsulinemia has been shown to mimic tumor cell proliferation via the insulin-like growth factor-1 (IGF-1) cascade (90, 91). In fact, the IGF-1 pathway has been shown to promote astrocyte proliferation, and studies suggest overactivation of the IGF-1 pathway is linked to greater GBS invasiveness and poor outcomes (90–92). Consequently, silencing of IGF-binding protein-2 has been shown to inhibit invasiveness in human GBS cells (93).

Corticosteroid contraindications

As mentioned earlier, glucocorticoid-induced hyperglycemia remains a concern in the treatment of GBS. Glucocorticoid use has been linked to poorer overall survival outcomes in several studies (2, 94). For example, Welch and Grommes suggested that steroid use could independently predict shorter overall survival. They showed that T2DM patients who remained steroid-dependent lived 8 months less than those who were tapered off steroid therapy (64).

However, this area is still controversial as it is those with greater symptoms, typically, who require corticosteroid therapy. As a result, an examination of the relationship may be muddled because those receiving corticosteroid therapy may have a more aggressive disease state Even then, Chaichana and colleagues demonstrated that the negative prognostic value of corticosteroid use was not dependent on tumor size (95).

Furthermore, Caramanna showed that corticosteroid use was linked to poorer outcomes in memory function, expressive language, and executive function compared to GBS cohorts not using corticosteroids (96). Accordingly, many clinical trials for GBS have corticosteroid use as an exclusion criterion. This may, however, artificially inflate overall survival values in these studies compared to historical literature. Taken together, current literature suggests corticosteroids, if used, should be closely monitored

by endocrinology and tapered in use for comorbid GBS patients with diabetes.

Emerging treatments

As mentioned earlier, the standard practices for treating patients diagnosed with cranial tumors are surgical resection, chemotherapy/radiotherapy, and corticosteroid therapy. However, treating high-grade gliomas in patients with DM tends to be complex due to the potential impact of the IGF-1 signaling pathway in hyperinsulinemic patients (97, 98). Prior studies have shown that the invasiveness of GBS can be associated with hyperactivity of the IGF-1 pathway (90, 99).

Furthermore, corticosteroid treatment in DM patients has been shown to be contraindicated due to blood glucose disruption and its association with induced hyperglycemia, which can potentially contribute to worse outcomes in cranial tumor patients (100). Due to the difficulty in treating these patients, advancements have aimed to provide approaches to circumvent this issue. Recent research has shown that a somatostatin analog that regulates the IGF-1 pathway has the potential to reduce glioblastoma growth in various models (101).

Both doxorubicin (DOX) and AN-162 demonstrated inhibition of cell proliferation and prolonging of tumor doubling time in this context, suggesting potential for clinical use in patients suffering from cranial tumors (101). Similarly, the IGF-1R inhibitor picropodophyllin (PPP) has demonstrated similar effects (102). Further, studies have revealed that cell lines are highly sensitive to PPP and that it inhibits progression of the cell cycle—potentially through necrosis—contributing to its potency (103). Further, PPP's ability to permeate the blood–brain barrier (BBB) and lack of long-term adverse effects in animals suggests the possibility of progression as a future treatment for cranial tumors, specifically in patients with DM.

The lack of flexibility of cranial tumors in using glucose and ketone bodies for energy, compared to normal brain tissue, is where novel approaches are primarily focused (102, 104–106). The ability to lower blood glucose while raising ketone bodies allows for specific tumor targeting. Due to the crucial need for strict glucose control, as it has been seen to improve overall survival in these patients, recent studies have emphasized the need for a proper and unique diet built for optimal glycemic control. The ketogenic diet (KD), also known as ketogenic metabolic therapy (KMT), is defined by the inclusion of fat-rich foods with the exclusion of carbohydrate-rich foods. Together, this diet alteration was the initial attempt to alleviate the potential burden of hyperglycemia for malignant brain cancer (107). Due to the lack of sugars in the diet, the intent was to induce ketone body use for energy rather than glucose, which would mitigate the impact of the Warburg effect. Further observation of the tumor site through positron emission tomography with
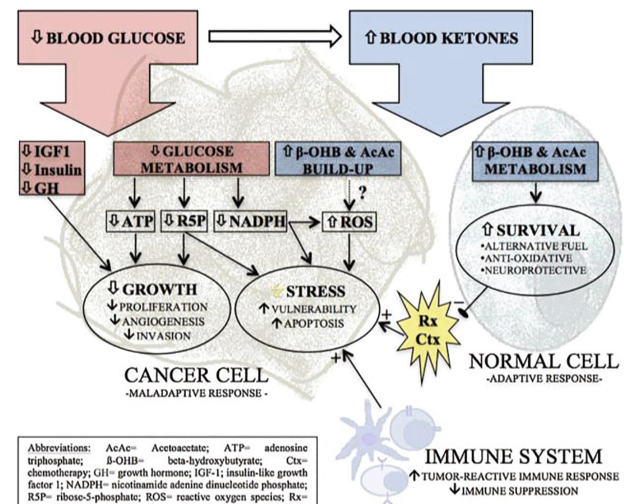

FIGURE 5 | Proposed cellular mechanisms of ketogenic diet's associated antineoplastic effects. The ketogenic diet (KD) is aimed at lowering glycemic levels and inducing ketosis to differentially affect the metabolism of cancer cells. Together, a deficit in glucose-derived ATP synthesis, reduced nucleotide biosynthesis, and absent redox potential drive malignant cells toward an apoptotic state that is then vulnerable to Rx/Ctx treatment. Concurrently, a decline of systemic levels of IGF-1, insulin, and GH diminish tumorigenicity and metastaticity by inhibiting pro-survival stimuli via Akt/mTOR and Ras/MAPK pathway modulation. Due to insufficient enzymatic machinery, cancer cells will inadequately metabolize ketone bodies (KB)—namely, ß-OHB and AcAc—which will then lead to their subsequent accumulation and further increase proapoptotic stimuli via ROS signaling. Conversely, KBs are efficiently metabolized by non-pathologic brain parenchyma and are thought to induce a neuroprotective state that may prevent metastasis and potentially attenuate damage due to Rx/Ctx treatment. Finally, KD has demonstrated immune-boosting effects through alleviating immune suppression and increasing tumor-reactive immune response (111).

flurodeoxyglucose showed a significant reduction in glucose uptake (107).

Additionally, studies have shown the anticonvulsant and antiepileptic effect of KD, which would be effective in reducing the need for concomitant glucocorticoid therapy (108). Similarly, diet restriction also provides an anti-angiogenic effect due to a reduction in tumor metabolism (104, 109). The combination of a lack of cerebral blood flow and a lack of glucose for energy can further reduce tumor growth and emphasize apoptosis (110). However, there are many other proposed mechanisms involved when discussing the utility of the KD, as can be seen in **Figure 5**.

Although the recent advancements have shown promise, far more research must be conducted in larger human populations before they can have any definite effect clinically. Novel advancements and emerging treatments are lacking in the context of patients with DM diagnosed with cranial tumors. Given the substantial increase in the prevalence of DM in the United States, it is imperative that further research focus on therapeutics that circumvent the contraindications for cranial tumor therapy in DM patients (112).

Conclusion

In this review, we identified a clear negative association between hyperglycemia, a major consequence of DM, and its impact on GBS progression and patient prognosis. We first explained the metabolic mechanisms behind this relationship, principally the Warburg effect, and proceeded to highlight the importance of glycemic control to curb its effects via standard-of-care options such as metformin administration. Of importance, we also underlined the contraindication consistently observed in preclinical and clinical trials regarding corticosteroid pharmacotherapy's pronounced effect on patient blood glucose levels.

Moreover, the potential ramifications of such blood glucose elevations were explained to be implicated in the alteration of several intracellular pathways, as explained earlier, as well as increased insulin levels. Although contraindicated in the context of its hyperglycemic-inducing effects, especially in comorbid DM patients, the literature supports corticosteroid use when used in conjunction with good glycemic control and frequent endocrinology consultation.

Additionally, we introduced recent interventions targeted at the IGF-1 pathway via the administration of somatostatin analogs, such as DOX and AN-162, and an IGF-1R inhibitor known as PPP. Individually, these drugs have shown promise in their ability to alleviate GBS growth. Finally, a more novel approach targeted at the Warburg effect itself, via a diet modification to the KD, was explained.

Author contributions

MF, AP, SS, and AR prepared the original draft. BL-W reviewed and edited. All authors contributed to the article and approved the submitted version.

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